1 Tradename(s)

Pluvicto® 1 GBq/mL (27 mCi/mL) solution for injection/infusion

2 Description and composition

Pharmaceutical form

Solution for injection/infusion.

Clear, colorless to slightly yellow solution.

pH: 4.5 to 7.0.

Active substance

One mL of solution contains 1 GBq (27 mCi) of lutetium (^{177}Lu) vipivotide tetraxetan at the date and time of calibration.

The total amount of radioactivity per single-dose vial is 7.4 GBq (200 mCi) ± 10% at the date and time of administration. Given the fixed volumetric activity of 1 GBq/mL (27 mCi) at the date and time of calibration, the volume of the solution in the vial can range from 7.5 mL to 12.5 mL in order to provide the required amount of radioactivity at the date and time of administration.

Physical characteristics

Lutetium-177 decays to a stable hafnium-177 with a physical half-life of 6.647 days by emitting beta-minus radiation with a maximum energy of 0.498 MeV (79%) and photonic radiation (γ) of 0.208 MeV (11%) and 0.113 MeV (6.4%).

The main radiations of lutetium-177 are detailed in Table 2-1.

Table 2-1 Lutetium-177 Main Radiations

Radiation	Energy (keV)	Iβ-%	Iγ%
β-	176.5	12.2	
β-	248.1	0.05	
β-	384.9	9.1	
β-	497.8	78.6	
γ	71.6		0.15
γ	112.9		6.40
γ	136.7		0.05
γ	208.4		11.0
γ	249.7		0.21

Radiation	Energy (keV)	Iβ-%	Iγ%
γ	321.3		0.22

External radiation

Table 2-2 summarizes the radioactive decay properties of lutetium-177.

Table 2-2 Physical Decay Chart: Lutetium-177 Physical Half-life = 6.647 days

Hours	Fraction Remaining
0	1.000
1	0.996
2	0.991
5	0.979
10	0.958
24 (1 day)	0.901
48 (2 days)	0.812
72 (3 days)	0.731
120 (5 days)	0.594
168 (7 days)	0.482
336 (14 days)	0.232
720 (30 days)	0.044
1080 (45 days)	0.009

Excipients

Acetic acid (0.30 mg/mL), sodium acetate (0.41 mg/mL), gentisic acid (0.39 mg/mL), sodium ascorbate (50.0 mg/mL), pentetic acid (0.10 mg/mL), water for injections (q.s. to 1 mL).

Each mL of solution contains up to 0.312 mmol (7.1 mg) of sodium.

3 Indications

Pluvicto® is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibitor and taxane-based chemotherapy.

4 Dosage regimen and administration

Important safety instructions

Pluvicto is a radiopharmaceutical and should be handled with appropriate safety measures to minimize radiation exposure (see section 6 Warnings and precautions). Waterproof gloves and effective radiation shielding should be used when handling Pluvicto.

Radiopharmaceuticals, including Pluvicto, should be used by or under the control of healthcare providers who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals.

Patient identification

Patients should be identified for treatment by PSMA imaging.

Dosage regimen

The recommended Pluvicto dose is 7.4 GBq (200 mCi) intravenously every 6 weeks (± 1 week) for a total of 6 doses.

Treatment monitoring

Laboratory tests should be performed before and during treatment with Pluvicto.

- Hematology (hemoglobin, white blood cell count, absolute neutrophil count, platelet count)
- Kidney function (serum creatinine, calculated creatinine clearance [CLcr])
- Liver function (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood serum albumin, total blood bilirubin)

Dose modifications for adverse drug reactions

Recommended dose modifications of Pluvicto for adverse drug reactions are provided in Table 4-1. Management of severe or intolerable adverse drug reactions may require temporary dose interruption (extending the dosing interval by 4 weeks from 6 weeks up to 10 weeks), dose reduction or permanent discontinuation of treatment with Pluvicto. If a treatment delay due to an adverse drug reaction persists for >4 weeks, treatment with Pluvicto must be discontinued. The dose of Pluvicto may be reduced by 20% once; the dose should not be re-escalated. If a patient has further adverse drug reactions that would require an additional dose reduction, treatment with Pluvicto must be discontinued.

Table 4-1 Recommended dose modifications of Pluvicto for adverse drug reactions

Adverse drug reaction	Severity[a]	Dose modification
Dry mouth	Grade ≥3	Reduce Pluvicto dose by 20%.
Gastrointestinal toxicity	Grade ≥3 (not amenable to medical intervention)	Withhold Pluvicto until improvement to Grade 2 or baseline. Reduce Pluvicto dose by 20%.
Anemia, thrombocytopenia, leukopenia, neutropenia, pancytopenia	Grade 2	Withhold Pluvicto until improvement to Grade 1 or baseline. Manage as deemed appropriate. The use of growth factors is permitted but should be discontinued once improved to Grade 1 or baseline. Checking hematinic levels (iron, B12, and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated.
	Grade ≥3	Withhold Pluvicto until improvement to Grade 1 or baseline. Reduce Pluvicto dose by 20%.
Renal toxicity	Defined as: • Confirmed serum creatinine increase (Grade ≥2)	Withhold Pluvicto until improvement.

Adverse drug reaction	Severity[a]	Dose modification
	• Confirmed CLcr <30 mL/min; calculate using Cockcroft-Gault with actual body weight	
	Defined as: • Confirmed ≥40% increase from baseline serum creatinine and • Confirmed >40% decrease from baseline CLcr; calculate using Cockcroft-Gault with actual body weight	Withhold Pluvicto until improvement or return to baseline. Reduce Pluvicto dose by 20%.
	Recurrent renal toxicity (Grade ≥3)	Permanently discontinue Pluvicto.
Spinal cord compression	Any	Withhold Pluvicto until the compression has been adequately treated and any neurological sequela have stabilized and ECOG performance status has stabilized.
Fracture in weight-bearing bones	Any	Withhold Pluvicto until the fracture has been adequately stabilized/treated and ECOG performance status has stabilized.
AST or ALT elevation	AST or ALT >5 times ULN in the absence of liver metastases	Permanently discontinue Pluvicto.

Abbreviations: CLcr, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal.

Grading according to most current Common Terminology Criteria for Adverse Events (CTCAE).

[a]The same thresholds are also applicable to baseline values at the time of treatment initiation with Pluvicto.

Special populations

Renal impairment

Exposure of Pluvicto is expected to increase with the degree of renal impairment. Patients with mild or moderate renal impairment may be at greater risk of toxicity. No dose adjustment is recommended for patients with mild renal impairment (baseline CLcr 60 to 89 mL/min by Cockcroft-Gault); however, insufficient data are available for drawing a conclusion for patients with moderate renal impairment (CLcr 30 to 59 mL/min). Renal function and adverse reactions should be monitored frequently in patients with mild to moderate renal impairment. The pharmacokinetic profile and safety of Pluvicto have not been studied in patients with severe (CLcr 15 to 29 mL/min) renal impairment or end-stage renal disease.

Hepatic impairment

No dose adjustment is recommended for patients with hepatic impairment.

Pediatric patients (below 18 years of age)

The safety and effectiveness of Pluvicto in pediatric patients have not been established.

Geriatric patients (65 years of age or older)

No dose adjustment is recommended in patients 65 years or older.

Method of administration

Preparation instructions

- Aseptic technique and radiation shielding should be used when handling or administering Pluvicto, using tongs as needed to minimize radiation exposure.
- The vial should be visually inspected under a shielded screen for particulate matter and discoloration prior to administration. The vial should be discarded if particulates or discoloration are present.
- Pluvicto is a ready-to-use solution for single use only. The Pluvicto solution should not be injected directly into any other intravenous solution.
- The amount of radioactivity delivered to the patient should be confirmed with an appropriately calibrated dose calibrator prior to and after Pluvicto administration.
- Any unused medicinal product or waste material should be disposed of in accordance with national regulations.

Administration instructions

The recommended dose of Pluvicto may be administered intravenously as an injection using a disposable syringe fitted with a syringe shield (with or without a syringe pump), as an infusion using the gravity method (with or without an infusion pump), or as an infusion using the vial (with a peristaltic infusion pump).

A reduced dose of Pluvicto should be administered using the syringe method (with or without a syringe pump) or the vial method (with a peristaltic infusion pump). Using the gravity method to administer a reduced dose of Pluvicto is not recommended since it may result in delivery of the incorrect volume of Pluvicto if the dose is not adjusted prior to administration.

Prior to administration, flush the intravenous catheter used exclusively for Pluvicto administration with ≥10 mL of 0.9% sterile sodium chloride solution to ensure patency and to minimize the risk of extravasation. Cases of extravasation should be managed as per institutional guidelines.

Intravenous methods of administration

Instructions for the syringe method (with or without a syringe pump)

- After disinfecting the vial stopper, withdraw an appropriate volume of Pluvicto solution to deliver the desired radioactivity by using a disposable syringe fitted with a syringe shield and a disposable sterile needle.
- Administer Pluvicto to the patient by slow intravenous push within approximately 1 to 10 minutes (either with a syringe pump or manually without a syringe pump) via an intravenous catheter that is pre-filled with 0.9% sterile sodium chloride solution and that is used exclusively for Pluvicto administration to the patient.
- Once the desired Pluvicto radioactivity has been administered, perform an intravenous flush of ≥10 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

Instructions for the gravity method (with or without an infusion pump)

- Insert a 2.5 cm, 20 gauge needle (short needle) into the Pluvicto vial and connect via a catheter to 500 mL 0.9% sterile sodium chloride solution (used to transport the Pluvicto solution during the infusion). Ensure that the short needle does not touch the Pluvicto solution in the vial and do not connect the short needle directly to the patient. Do not allow

the sodium chloride solution to flow into the Pluvicto vial prior to the initiation of the Pluvicto infusion and do not inject the Pluvicto solution directly into the sodium chloride solution.

- Insert a second needle that is 9 cm, 18 gauge (long needle) into the Pluvicto vial, ensuring that the long needle touches and is secured to the bottom of the Pluvicto vial during the entire infusion. Connect the long needle to the patient by an intravenous catheter that is pre-filled with 0.9% sterile sodium chloride solution and that is used exclusively for the Pluvicto infusion into the patient.
- Use a clamp or an infusion pump to regulate the flow of the sodium chloride solution via the short needle into the Pluvicto vial (the sodium chloride solution entering the vial through the short needle will carry the Pluvicto solution from the vial to the patient via the intravenous catheter connected to the long needle within approximately 30 minutes).
- During the infusion, ensure that the level of solution in the Pluvicto vial remains constant.
- Disconnect the vial from the long needle line and clamp the saline line once the level of radioactivity is stable for at least five minutes.
- Follow the infusion with an intravenous flush of ≥10 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

Instructions for the vial method (with a peristaltic infusion pump)

- Insert a 2.5 cm, 20 gauge needle (short venting needle) into the Pluvicto vial. Ensure that the short needle does not touch the Pluvicto solution in the vial and do not connect the short needle directly to the patient or to the peristaltic infusion pump.
- Insert a second needle that is 9 cm, 18 gauge (long needle) into the Pluvicto vial, ensuring that the long needle touches and is secured to the bottom of the Pluvicto vial during the entire infusion. Connect the long needle and a 0.9% sterile sodium chloride solution to a 3-way stopcock valve via appropriate tubing.
- Connect the output of the 3-way stopcock valve to tubing installed on the input side of the peristaltic infusion pump following the pump manufacturer's instructions.
- Pre-fill the line by opening the 3-way stopcock valve and pumping the Pluvicto solution through the tubing until it reaches the exit of the valve.
- Pre-fill the intravenous catheter which will be connected to the patient by opening the 3-way stopcock valve to the 0.9% sterile sodium chloride solution and pumping the 0.9% sterile sodium chloride solution until it exits the end of the catheter tubing.
- Connect the pre-filled intravenous catheter to the patient and set the 3-way stopcock valve such that the Pluvicto solution is in line with the peristaltic infusion pump.
- Infuse an appropriate volume of Pluvicto solution at approximately 25 mL/h to deliver the desired radioactivity.
- When the desired Pluvicto radioactivity has been delivered, stop the peristaltic infusion pump and then change the position of the 3-way stopcock valve so that the peristaltic infusion pump is in line with the 0.9% sterile sodium chloride solution. Restart the peristaltic infusion pump and infuse an intravenous flush of ≥10 mL of 0.9% sterile sodium chloride solution through the intravenous catheter to the patient.

Radiation dosimetry

Dosimetry of lutetium (^{177}Lu) vipivotide tetraxetan was collected in 29 patients in the Phase III VISION sub-study, in order to calculate whole body and organ radiation dosimetry. The mean and standard deviation (SD) of the estimated radiation absorbed doses to different organs for

adult patients receiving Pluvicto are shown in Table 4-2. The organs with the highest radiation absorbed doses are lacrimal glands and salivary glands.

The maximum penetration of lutetium-177 in tissue is approximately 2 mm and the mean penetration is 0.67 mm.

Table 4-2 Estimated radiation absorbed dose for Pluvicto in the VISION sub-study

	Absorbed dose per unit activity (Gy/GBq)[a] (N = 29)		Calculated absorbed dose for 7.4 GBq administration (Gy)[a]		Calculated absorbed dose for 6 x 7.4 GBq (44.4 GBq cumulative activity) (Gy)[a]	
Organ	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Adrenals	0.033	0.025	0.24	0.19	1.5	1.1
Brain	0.007	0.005	0.049	0.035	0.30	0.22
Esophagus	0.025	0.026	0.18	0.19	1.1	1.1
Eyes	0.022	0.024	0.16	0.18	0.99	1.1
Gallbladder wall	0.028	0.026	0.20	0.19	1.2	1.1
Heart wall	0.17	0.12	1.2	0.83	7.8	5.2
Kidneys	0.43	0.16	3.1	1.2	19	7.3
Lacrimal glands	2.1	0.47	15	3.4	92	21
Left colon	0.58	0.14	4.1	1.0	26	6.0
Liver	0.090	0.044	0.64	0.32	4.0	2.0
Lungs	0.11	0.11	0.76	0.81	4.7	4.9
Osteogenic cells	0.036	0.028	0.26	0.21	1.6	1.3
Pancreas	0.027	0.026	0.19	0.19	1.2	1.1
Prostate	0.027	0.026	0.19	0.19	1.2	1.1
Red marrow	0.035	0.020	0.25	0.15	1.5	0.90
Rectum	0.56	0.14	4.0	1.1	25	6.2
Right colon	0.32	0.078	2.3	0.58	14	3.4
Salivary glands	0.63	0.36	4.5	2.6	28	16
Small intestine	0.071	0.031	0.50	0.23	3.1	1.4
Spleen	0.067	0.027	0.48	0.20	3.0	1.2
Stomach wall	0.025	0.026	0.18	0.19	1.1	1.1
Testes	0.023	0.025	0.16	0.18	1.0	1.1
Thymus	0.025	0.026	0.18	0.19	1.1	1.1
Thyroid	0.26	0.37	1.8	2.7	11	16
Total body	0.037	0.027	0.27	0.20	1.6	1.2

Urinary bladder wall	0.32	0.025	2.3	0.19	14	1.1

[a]Values have been calculated based on dosimetry estimates at full precision and rounded to relevant digits.

5 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 2 Description and composition.

6 Warnings and precautions

Risk from radiation exposure

Pluvicto contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer.

Radiation exposure to patients, medical personnel, and household contacts should be minimized during and after treatment with Pluvicto consistent with institutional good radiation safety practices, patient management procedures, and instructions to the patient for follow-up radiation protection at home.

Patients should be encouraged to increase oral fluids and urged to void as often as possible to reduce bladder radiation, especially after high activities, e.g. radionuclide therapy.

Before the patient is released, the nuclear medicine physician or healthcare provider should explain the necessary radioprotection precautions that the patient should follow to minimize radiation exposure to others.

Following administration of Pluvicto, patients should be advised to:

- limit close contact (less than 1 meter) with household contacts for 2 days or with children and pregnant women for 7 days.
- Refrain from sexual activity for 7 days.
- sleep in a separate bedroom from household contacts for 3 days, from children for 7 days, or from pregnant women for 15 days.

Myelosuppression

Pluvicto can cause severe and life-threatening myelosuppression, including anaemia, thrombocytopenia, leukopenia, and neutropenia. In the VISION study, myelosuppression occurred more frequently in patients who received Pluvicto plus best standard of care (BSoC) compared to patients who received BSoC alone (see section 7 Adverse drug reactions).

Hematology laboratory tests, including hemoglobin, white blood cell count, absolute neutrophil count, and platelet count, should be performed before and during treatment with Pluvicto. Pluvicto should be withheld, dose reduced, or permanently discontinued and patients should be clinically managed as deemed appropriate based on the severity of myelosuppression (see section 4 Dosage regimen and administration).

Renal toxicity

In the VISION study, renal toxicity occurred more frequently in patients who received Pluvicto plus BSoC compared to patients who received BSoC alone (see section 7 Adverse drug reactions).

Patients should be advised to remain well hydrated and to urinate frequently before and after administration of Pluvicto. Kidney function laboratory tests, including serum creatinine and calculated CLcr, should be performed before and during treatment with Pluvicto. Pluvicto should be withheld, dose reduced, or permanently discontinued based on the severity of renal toxicity (see section 4 Dosage regimen and administration).

7 Adverse drug reactions

Summary of the safety profile

The safety of Pluvicto was evaluated in the Phase III VISION study in patients with progressive, PSMA-positive mCRPC. Of the 831 patients randomized, 734 patients received at least one dose of randomized treatment. Patients received at least one dose of either Pluvicto 7.4 GBq (200 mCi) administered every 6 to 10 weeks plus BSoC (N = 529) or BSoC alone (N = 205).

Among patients who received Pluvicto plus BSoC, the median number of doses of Pluvicto received was 5 (range: 1 to 6), with 67.7% of patients who received at least 4 doses of Pluvicto and 46.5% of patients who received a total of 6 doses of Pluvicto. The median cumulative dose of Pluvicto was 37.5 GBq (range: 7.0 to 48.3). The median duration of exposure to randomized treatment was 7.8 months (range: 0.3 to 24.9) for patients who received Pluvicto plus BSoC and 2.1 months (range: 0.0 to 26.0) for patients who received BSoC alone.

Table 7-1 summarizes the incidence of adverse drug reactions. The most common adverse drug reactions (≥20%) occurring at a higher incidence in patients who received Pluvicto plus BSoC compared to BSoC alone include: fatigue (43.1%), dry mouth (39.3%), nausea (35.3%), anaemia (31.8%), decreased appetite (21.2%), and constipation (20.2%). The most common Grade 3 to 4 adverse drug reactions (≥5%) occurring at a higher incidence in patients who received Pluvicto plus BSoC compared to BSoC alone include: anaemia (12.9%), thrombocytopenia (7.9%), lymphopenia (7.8%), and fatigue (5.9%).

Tabulated summary of adverse drug reactions

Adverse drug reactions (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7-1 Adverse drug reactions occurring at a higher incidence in patients who received Pluvicto plus BSoC compared to BSoC alone in VISION[a]

	Pluvicto plus BSoC (N = 529)			BSoC (N = 205)		
Adverse drug reactions	**All grades n (%)**	**Frequency category**	**Grades 3 to 4[b] n (%)**	**All grades n (%)**	**Frequency category**	**Grades 3 to 4[b] n (%)**
Blood and lymphatic system disorders						
Anaemia	168 (31.8%)	Very common	68 (12.9%)	27 (13.2%)	Very common	10 (4.9%)
Thrombocytopenia	91 (17.2%)	Very common	42 (7.9%)	9 (4.4%)	Common	2 (1.0%)
Leukopenia[c]	83 (15.7%)	Very common	22 (4.2%)	4 (2.0%)	Common	1 (0.5%)
Lymphopenia	75 (14.2%)	Very common	41 (7.8%)	8 (3.9%)	Common	1 (0.5%)
Pancytopenia[d]	9 (1.7%)	Common	7 (1.3%)[b]	0		0
Nervous system disorders						
Dizziness	44 (8.3%)	Common	5 (0.9%)	9 (4.4%)	Common	0
Headache	37 (7.0%)	Common	4 (0.8%)	4 (2.0%)	Common	0
Dysgeusia[e]	37 (7.0%)	Common	0	3 (1.5%)	Common	0
Eye disorders						
Dry eye	16 (3.0%)	Common	0	2 (1.0%)	Uncommon	0
Ear and labyrinth disorders						
Vertigo	11 (2.1%)	Common	0	0		0
Gastrointestinal disorders						
Dry mouth[f]	208 (39.3%)	Very common	0	1 (0.5%)	Uncommon	0
Nausea	187 (35.3%)	Very common	7 (1.3%)	34 (16.6%)	Very common	1 (0.5%)
Constipation	107 (20.2%)	Very common	6 (1.1%)	23 (11.2%)	Very common	1 (0.5%)
Vomiting[g]	101 (19.1%)	Very common	5 (0.9%)	13 (6.3%)	Common	1 (0.5%)
Diarrhoea	100 (18.9%)	Very common	4 (0.8%)	6 (2.9%)	Common	1 (0.5%)
Abdominal pain[h]	59 (11.2%)	Very common	6 (1.1%)	13 (6.3%)	Common	1 (0.5%)
Renal and urinary disorders						
Urinary tract infection[i]	61 (11.5%)	Very common	20 (3.8%)	2 (1.0%)	Uncommon	1 (0.5%)
Acute kidney injury[j]	45 (8.5%)	Common	17 (3.2%)	12 (5.9%)	Common	6 (2.9%)
General disorders and administration site conditions						
Fatigue	228 (43.1%)	Very common	31 (5.9%)	47 (22.9%)	Very common	3 (1.5%)
Decreased appetite	112 (21.2%)	Very common	10 (1.9%)	30 (14.6%)	Very common	1 (0.5%)
Weight decreased	57 (10.8%)	Very common	2 (0.4%)	18 (8.8%)	Common	0

	Pluvicto plus BSoC (N = 529)			BSoC (N = 205)		
Adverse drug reactions	**All grades n (%)**	**Frequency category**	**Grades 3 to 4[b] n (%)**	**All grades n (%)**	**Frequency category**	**Grades 3 to 4[b] n (%)**
Oedema peripheral[k]	52 (9.8%)	Common	2 (0.4%)	14 (6.8%)	Common	(0.5%)
Pyrexia	36 (6.8%)	Common	2 (0.4%)	7 (3.4%)	Common	0

Abbreviation: BSoC, best standard of care.

[a]National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

[b]Only includes Grades 3 to 4 adverse drug reactions, with the exception of pancytopenia. Grade 5 (fatal) pancytopenia was reported in 2 patients who received Pluvicto plus BSoC.

[c]Leukopenia includes leukopenia and neutropenia.

[d]Pancytopenia includes pancytopenia and bicytopenia.

[e]Dysgeusia includes dysgeusia and taste disorder.

[f]Dry mouth includes dry mouth, aptyalism, and dry throat.

[g]Vomiting includes vomiting and retching.

[h]Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and gastrointestinal pain.

[i]Urinary tract infection includes urinary tract infection, cystitis, and cystitis bacterial.

[j]Acute kidney injury includes blood creatinine increased, acute kidney injury, renal failure, and blood urea increased.

[k]Oedema peripheral includes oedema peripheral, fluid retention, and fluid overload.

Description of selected adverse drug reactions

Myelosuppression

In the VISION study, myelosuppression occurred more frequently in patients who received Pluvicto plus BSoC compared to patients who received BSoC alone (all Grades/Grade ≥3: anemia (31.8%/12.9%) versus (13.2%/4.9%); thrombocytopenia (17.2%/7.9%) versus (4.4%/1.0%); leukopenia (12.5%/2.5%) versus (2.0%/0.5%); lymphopenia (14.2%/7.8%) versus (3.9%/0.5%); neutropenia (8.5%/3.4%) versus (1.5%/0.5%); pancytopenia (1.5%/1.1%) versus (0%/0%) including two fatal events of pancytopenia in patients who received Pluvicto plus BSoC; and bicytopenia (0.2%/0.2%) versus (0%/0%).

Myelosuppression adverse drug reactions that led to permanent discontinuation in ≥0.5% of patients who received Pluvicto plus BSoC included: anemia (2.8%), thrombocytopenia (2.8%), leukopenia (1.3%), neutropenia (0.8%), and pancytopenia (0.6%). Myelosuppression adverse drug reactions that led to dose interruptions /dose reductions in ≥0.5% of patients who received Pluvicto plus BSoC included: anemia (5.1%/1.3%), thrombocytopenia (3.6%/1.9%), leukopenia (1.5%/0.6%), and neutropenia (0.8%/0.6%).

Renal toxicity

In the VISION study, renal toxicity occurred more frequently in patients who received Pluvicto plus BSoC compared to patients who received BSoC alone (all Grades/Grades 3 to 4): blood creatinine increased (5.3%/0.2%) versus (2.4%/0.5%); acute kidney injury (3.6%/3.0%) versus (3.9%/2.4%); renal failure (0.2%/0%) versus (0%/0%); and blood urea increased (0.2%/0%) versus (0%/0%).

Renal adverse drug reactions that led to permanent discontinuation in ≥0.2% of patients who received Pluvicto plus BSoC included: blood creatinine increased (0.2%). Renal adverse drug reactions that led to dose interruptions /dose reductions in ≥0.2% of patients who received Pluvicto plus BSoC included: blood creatinine increased (0.2%/0.4%) and acute kidney injury (0.2%/0%).

8 Interactions

No clinical drug interaction studies were performed.

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

The safety and efficacy of Pluvicto have not been established in females as Pluvicto is not indicated for use in females. No animal studies using lutetium (^{177}Lu) vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including Pluvicto, have the potential to cause fetal harm. Based on its mechanism of action, Pluvicto can cause fetal harm when administered to a pregnant woman (see section 11 Clinical pharmacology).

9.2 Lactation

Risk summary

The safety and efficacy of Pluvicto have not been established in females as Pluvicto is not indicated for use in females. There are no data on the presence of lutetium (^{177}Lu) vipivotide tetraxetan in human milk or its effects on the breastfed child or on milk production.

9.3 Females and males of reproductive potential

Contraception

Males

Based on its mechanism of action, male patients should be advised not to father a child and to use condoms for intercourse during treatment with Pluvicto and for 14 weeks after the last dose (see section 11 Clinical pharmacology, section 13 Non-clinical safety data).

Infertility

No studies were conducted to determine the effects of lutetium (^{177}Lu) vipivotide tetraxetan on fertility. The recommended cumulative dose of 44.4 GBq of Pluvicto results in a radiation absorbed dose to the testes within the range where Pluvicto may cause infertility.

10 Overdosage

In the event of administration of a radiation overdose with Pluvicto, the radiation absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding. It might be helpful to estimate the effective radiation dose that was applied.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Other therapeutic radiopharmaceuticals, ATC code: V10XX05

Mechanism of action (MOA)

The active moiety of Pluvicto is the radionuclide lutetium-177 which is linked to a targeting moiety that binds with high affinity to PSMA, a transmembrane protein that is highly expressed in prostate cancer, including mCRPC. Upon the binding of Pluvicto to PSMA-expressing cancer cells, the beta-minus emission from lutetium-177 delivers therapeutic radiation to the targeted cell, as well as to surrounding cells, and induces DNA damage which can lead to cell death.

Pharmacodynamics (PD)

There are no data regarding lutetium (^{177}Lu) vipivotide tetraxetan exposure-efficacy relationships and the time course of pharmacodynamic response.

There are limited data regarding lutetium (^{177}Lu) vipivotide tetraxetan exposure-safety relationships and the time course of pharmacodynamic response.

Unlabeled vipivotide tetraxetan does not have any pharmacodynamic activity.

Cardiac electrophysiology

The ability of Pluvicto to prolong the QTc interval at the recommended dose was assessed in 30 patients in the Phase III VISION sub-study. Pluvicto did not prolong the QT/QTc interval.

Pharmacokinetics (PK)

The pharmacokinetics of lutetium (^{177}Lu) vipivotide tetraxetan have been characterized in 30 patients in the Phase III VISION sub-study.

Absorption

Pluvicto is administered intravenously and is immediately and completely bioavailable.

The geometric mean blood exposure (area under the curve [AUC_{inf}]) for lutetium (^{177}Lu) vipivotide tetraxetan at the recommended dose is 52.3 ng.h/mL (geometric mean coefficient of variation [CV] 31.4%). The geometric mean maximum blood concentration (C_{max}) for lutetium (^{177}Lu) vipivotide tetraxetan is 6.58 ng/mL (CV 43.5%).

Distribution

The geometric mean volume of distribution (V_z) for lutetium (^{177}Lu) vipivotide tetraxetan is 123 L (CV 78.1%).

Unlabeled vipivotide tetraxetan and non-radioactive lutetium (^{175}Lu) vipivotide tetraxetan are each 60% to 70% bound to human plasma proteins.

Organ uptake

The biodistribution of lutetium (^{177}Lu) vipivotide tetraxetan shows primary uptake in lacrimal glands, salivary glands, kidneys, urinary bladder wall, liver, small intestine, and large intestine (left and right colon).

Elimination

The geometric mean clearance (CL) for lutetium (^{177}Lu) vipivotide tetraxetan is 2.04 L/h (CV 31.5%).

Half-life

Pluvicto shows a bi-exponential elimination with a geometric mean terminal elimination half-life (T½) of 41.6 hours (CV 68.8%).

Metabolism

Lutetium (^{177}Lu) vipivotide tetraxetan does not undergo hepatic or renal metabolism.

Excretion

Lutetium (^{177}Lu) vipivotide tetraxetan is primarily eliminated renally.

Special populations

Geriatric patients (65 years of age or older)

Of the 529 patients who received at least one dose of Pluvicto plus BSoC in the VISION study, 387 patients (73%) were 65 years or older and 143 patients (27%) were 75 years or older.

Age/Body weight

No clinically significant effects on the pharmacokinetic parameters of lutetium (^{177}Lu) vipivotide tetraxetan were identified for the following covariates assessed in 30 patients in the Phase III VISION sub-study: age (median: 67 years; range: 52 to 80 years) and body weight (median: 88.8 kg; range: 63.8 to 143.0 kg).

Renal impairment

Based on population pharmacokinetic analysis, exposure of lutetium (^{177}Lu) vipivotide tetraxetan is expected to increase with the degree of renal impairment. Patients with mild or moderate renal impairment may be at greater risk of toxicity. No dose adjustment is recommended for patients with mild renal impairment (baseline CLcr 60 to 89 mL/min by Cockcroft-Gault); however, insufficient data are available for drawing a conclusion on patients with moderate renal impairment (CLcr 30 to 59 mL/min). Renal function and adverse reactions should be monitored frequently in patients with mild to moderate renal impairment. The effect of severe renal impairment (baseline CLcr 15 to 29 mL/min) or end-stage renal disease on lutetium (^{177}Lu) vipivotide tetraxetan pharmacokinetics has not been studied.

In vitro evaluation of drug interaction potential

CYP450 enzymes

Vipivotide tetraxetan is not a substrate of cytochrome P450 (CYP450) enzymes. It does not induce cytochrome P450 (CYP) 1A2, 2B6 or 3A4, and it does not inhibit cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4/5 *in vitro*.

Transporters

Vipivotide tetraxetan is not a substrate of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3 or OCT2, and it is not an inhibitor of BCRP, P-gp, BSEP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2 *in vitro*.

12 Clinical studies

The efficacy of Pluvicto in patients with progressive, PSMA-positive mCRPC was established in VISION, a randomized, multicenter, open-label Phase III study. Eight hundred and thirty-one (N = 831) patients were randomized (2:1) to receive either Pluvicto 7.4 GBq (200 mCi) every 6 weeks for up to a total of 6 doses plus BSoC (N = 551) or BSoC alone (N = 280).

Eligible patients were required to have PSMA-positive mCRPC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, at least one metastatic lesion present on computed tomography (CT), magnetic resonance imaging (MRI) or bone scan imaging, and adequate renal, hepatic and hematological function. Eligible patients were also required to have received at least one AR pathway inhibitor, such as abiraterone acetate or enzalutamide, and 1 or 2 prior taxane-based chemotherapy regimens (with a regimen defined as a minimum exposure of 2 cycles of a taxane). Patients with unstable symptomatic central nervous system metastases or symptomatic or clinically/radiologically impending spinal cord compression were not eligible for the study. Patients underwent a gallium (^{68}Ga) gozetotide positron emission tomography (PET) scan to evaluate PSMA expression in lesions defined by central read criteria. Eligible patients were required to have at least one PSMA-positive lesion identified by this scan, and no CT/MRI measurable lesions that showed poor or no gallium (^{68}Ga) gozetotide uptake on the PET scan.

BSoC administered at the physician's discretion included: supportive measures including pain medications, hydration, blood transfusions, etc.; ketoconazole; radiation therapy (including seeded form or any external beam radiotherapy [including stereotactic body radiotherapy and palliative external beam]) to localized prostate cancer targets; bone-targeted agents including zoledronic acid, denosumab, and any bisphosphonates; androgen-reducing agents including any corticosteroid and 5-alpha reductases; AR pathway inhibitors.

Patients continued randomized treatment until evidence of tumor progression (based on investigator assessment per Prostate Cancer Working Group 3 [PCWG3] criteria), unacceptable toxicity, use of prohibited treatment, non-compliance or withdrawal, or lack of clinical benefit.

The alternate primary efficacy endpoints were overall survival (OS) and radiographic progression-free survival (rPFS) by blinded independent central review (BICR) per PCWG3 criteria. Additional secondary efficacy endpoints were overall response rate (ORR) by BICR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and time to first symptomatic skeletal event (SSE) defined as first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain, or death from any cause, whichever occurred first.

Demographic and baseline disease characteristics were balanced between the treatment arms. The median age was 71 years (range: 40 to 94 years); 86.8% White; 6.6% Black or African American; 2.4% Asian; 92.4% had ECOG PS0-1; 7.6% had ECOG PS2. Randomization was stratified by baseline lactase dehydrogenase (LDH), presence of liver metastases, ECOG PS score and inclusion of an AR pathway inhibitor as part of BSoC at the time of randomization. At randomization, all patients (100.0%) had received at least one prior taxane-based chemotherapy regimen and 41.2% of patients had received two. At randomization, 51.3% of patients had received one prior AR pathway inhibitor, 41.0% of patients received 2, and 7.7% of patients had received 3 or more. During the randomized treatment period, 52.6% of patients in the Pluvicto plus BSoC arm and 67.8% of patients in the BSoC alone arm received at least one AR pathway inhibitor.

Efficacy results for VISION are presented in Table 12-1 and Figures 12-1 and 12-2. The final analyses of OS and rPFS were event-driven and conducted after the occurrence of 530 deaths

and 347 events, respectively. Treatment with Pluvicto plus BSoC demonstrated a statistically significant improvement in OS and rPFS by BICR compared to treatment with BSoC alone. The primary efficacy results are supported by a statistically significant difference between the treatment arms in the time to first SSE (p <0.001) and ORR (p <0.001). There was an estimated 38% risk reduction of death, an estimated 60% risk reduction of radiographic disease progression or death, and an estimated 50% risk reduction of SSE or death based on hazard ratios in favor of Pluvicto plus BSoC treatment.

Table 12-1 Efficacy results in VISION

Efficacy parameters	Pluvicto plus BSoC	BSoC
Alternate primary efficacy endpoints		
Overall survival (OS)	N = 551	N = 280
Deaths, n (%)	343 (62.3%)	187 (66.8%)
Median, months (95% CI)[a]	15.3 (14.2, 16.9)	11.3 (9.8, 13.5)
Hazard ratio (95% CI)[b]	0.62 (0.52, 0.74)	
P-value[c]	<0.001	
Radiographic progression-free survival (rPFS)[d]	N = 385	N = 196
Events (progression or death), n (%)	254 (66.0%)	93 (47.4%)
Radiographic progressions, n (%)	171 (44.4%)	59 (30.1%)
Deaths, n (%)	83 (21.6%)	34 (17.3%)
Median, months (99.2% CI)[a]	8.7 (7.9, 10.8)	3.4 (2.4, 4.0)
Hazard ratio (99.2% CI)[b]	0.40 (0.29, 0.57)	
P-value[c]	<0.001	
Secondary efficacy endpoints		
Time to first symptomatic skeletal event (SSE)	N = 385	N = 196
Events (SSE or death), n (%)	256 (66.5%)	137 (69.9%)
SSEs, n (%)	60 (15.6%)	34 (17.3%)
Deaths, n (%)	196 (50.9%)	103 (52.6%)
Median, months (95% CI)[a]	11.5 (10.3, 13.2)	6.8 (5.2, 8.5)
Hazard ratio (95% CI)[b]	0.50 (0.40, 0.62)	
P-value[e]	<0.001	
Best overall response (BOR)		
Patients with evaluable disease at baseline	N = 319	N = 120
Complete response (CR), n (%)	18 (5.6%)	0 (0%)
Partial response (PR), n (%)	77 (24.1%)	2 (1.7%)
Stable disease (SD), n (%)	68 (21.3%)	30 (25.0%)
Non-CR/Non-PD, n (%)	121 (37.9%)	48 (40.0%)
Progressive disease (PD), n (%)	33 (10.3%)	35 (29.2%)
Unknown, n (%)	2 (0.6%)	5 (4.2%)
Overall response rate (ORR)[f,g]	95 (29.8%)	2 (1.7%)
P-value[h]	<0.001	
Duration of response (DOR)[f]		
Number of responders	n = 95	n = 2
Events (progression or death), n (%)	46 (48.4%)	1 (50.0%)
Radiographic progressions, n (%)	29 (30.5%)	1 (50.0%)
Deaths, n (%)	17 (17.9%)	0 (0%)
Median, months (95% CI)[a]	9.8 (9.1, 11.7)	10.6 (NE, NE)[i]

Abbreviations: BSoC, best standard of care; CI: confidence interval; NE, not evaluable; BICR, blinded independent central review; PCWG3, prostate cancer working group 3; RECIST, response evaluation criteria in solid tumors.

[a]*Based on Kaplan-Meier estimate.*

Efficacy parameters	Pluvicto plus BSoC	BSoC

[b]*Hazard ratio based on the stratified Cox PH model. Hazard ratio <1 favors Pluvicto plus BSoC.*

[c]*Stratified log-rank test one-sided p-value.*

[d]*By BICR per PCWG3 criteria.*

[e]*Stratified log-rank test two-sided p-value.*

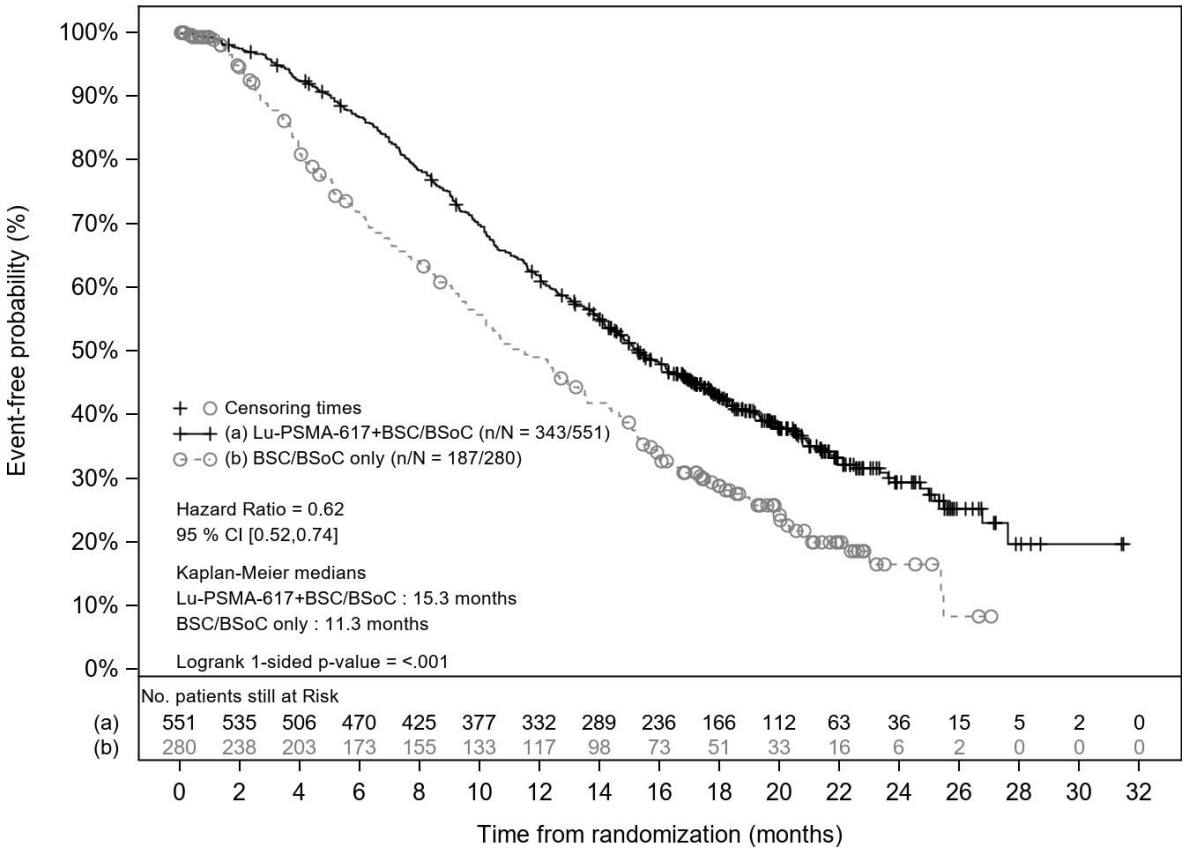
[f]*By BICR per RECIST v1.1.*

[g]*ORR: CR+PR. Confirmed response for CR and PR.*

[h]*Stratified Wald's Chi-square test two-sided p-value.*

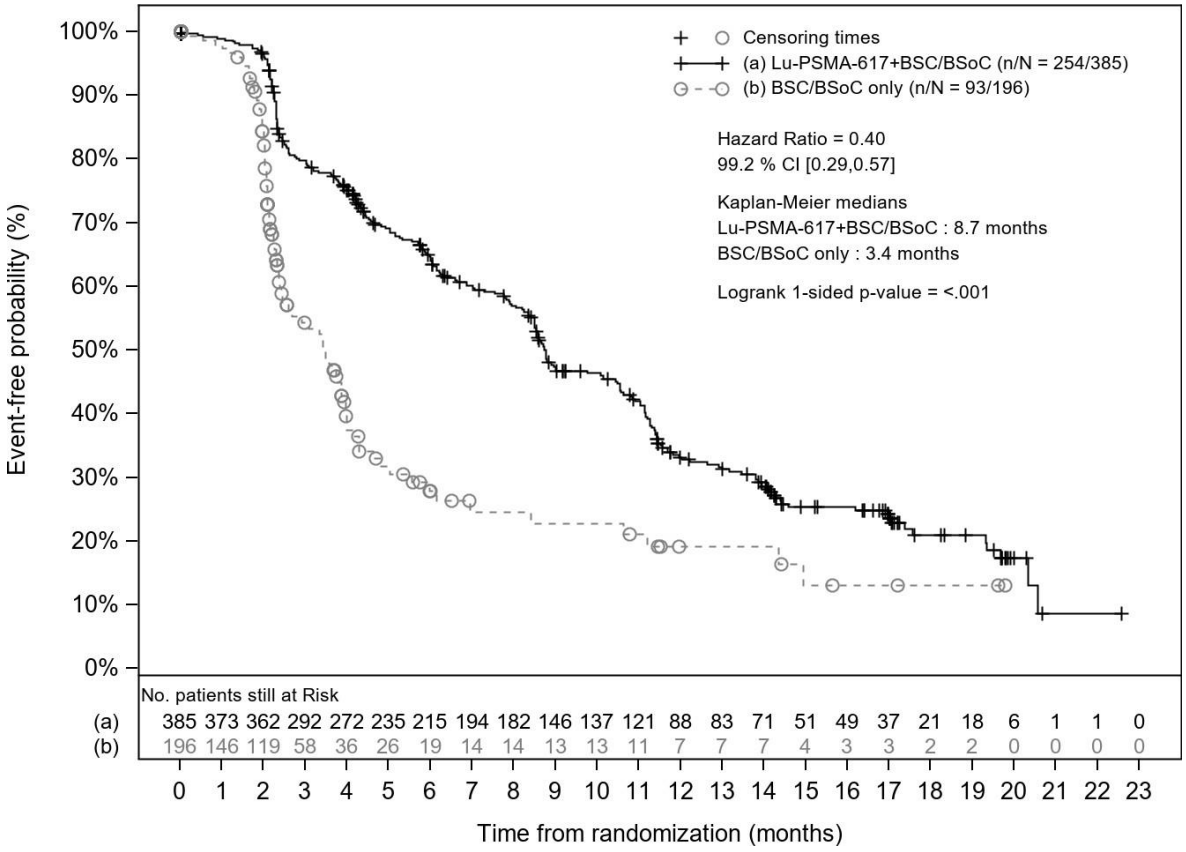
[i]*Median DOR in the BSoC only arm was not reliable since only 1 of the 2 patients who responded had RECIST v1.1 radiographic progression or death.*

Figure 12-1 Kaplan-Meier plot of overall survival in VISION



Stratified log-rank test and stratified Cox model using strata per Interactive Response Technology (IRT) defined by LDH level, presence of liver metastases, ECOG score and inclusion of an AR pathway inhibitor in BSoC at time of randomization.
n/N: Number of events/number of patients in treatment arm.

Figure 12-2 Kaplan-Meier plot of BICR-assessed radiographic progression-free survival (rPFS) in VISION



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of an AR pathway inhibitor in BSoC at time of randomization.
n/N: Number of events/number of patients in treatment arm.

Mean and median baseline prostate-specific antigen (PSA) levels were similar in both treatment arms. Serum PSA levels decreased by ≥50% from baseline in 177 of 385 (46.0%) patients who received Pluvicto plus BSoC and in 14 of 196 (7.1%) patients who received BSoC alone.

FACT-P total score showed an estimated 46% risk reduction of worsening from baseline, clinical progression or death based on hazard ratios in favor of Pluvicto plus BSoC, indicating patient stabilization and delay in time to deterioration while on Pluvicto plus BSoC treatment. Specifically, time to worsening of the FACT-P total score was delayed by 3.5 months for Pluvicto plus BSoC with a median time to deterioration of 5.7 months (95% CI: 4.8, 6.6) compared to 2.2 months (95% CI: 1.8, 2.8) for BSoC alone. BPI-SF pain intensity scale showed an estimated 48% risk reduction of worsening from baseline, clinical progression or death based on hazard ratios in favor of Pluvicto plus BSoC, indicating patient stabilization and less pain while on Pluvicto plus BSoC treatment. Specifically, time to worsening of the BPI-SF pain intensity scale was delayed by 3.7 months for Pluvicto plus BSoC with a median time to deterioration of 5.9 months (95% CI: 4.8, 6.9) compared to 2.2 months (95% CI: 1.8, 2.8) for BSoC alone. The results of these patient-reported outcomes (PRO) should be interpreted with caution in the context of the open-label study design. The proportion of patients with post-baseline PRO data available is higher in the Pluvicto plus BSoC arm as compared to the BSoC alone arm (e.g. 92.7% vs. 77.0% at Cycle 1, 88.1% vs. 52.0% at Cycle

2, 77.1% vs 27.6% at Cycle 3, 63.4% vs 16.3% at Cycle 4, 51.7% vs 10.7% at Cycle 5, and 44.7% vs. 6.6% at Cycle 6); these imbalances are related to shorter period of time on study treatment in the BSoC alone arm.

13 Non-clinical safety data

Safety pharmacology and animal toxicology

No toxicological effects were observed in safety pharmacology or single-dose toxicity studies in rats and minipigs administered a non-radioactive formulation containing unlabeled vipivotide tetraxetan and lutetium (^{175}Lu) vipivotide tetraxetan, or in repeat-dose toxicity studies in rats administered unlabeled vipivotide tetraxetan.

Carcinogenicity and mutagenicity

Mutagenicity and long-term carcinogenicity studies have not been carried out with lutetium (^{177}Lu) vipivotide tetraxetan; however, radiation is a carcinogen and mutagen.

Reproductive toxicity

For information on reproductive toxicity, see section 9 Pregnancy, lactation, females and males of reproductive potential.

14 Pharmaceutical information

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4 Dosage regimen and administration.

Shelf life

120 hours (5 days) from the date and time of calibration.

Special precautions for storage

Store below 30°C. Do not freeze. Store in the original package to protect from ionizing radiation (lead shielding).

Storage of radiopharmaceuticals should be in accordance with national regulations on radioactive materials.

Do not use Pluvicto after the expiry date and time which are stated on the label after EXP.

Nature and contents of container

Clear, colorless type I glass vial, closed with a bromobutyl rubber stopper and aluminum seal.

Each vial contains a volume of solution that can range from 7.5 mL to 12.5 mL corresponding to a radioactivity of 7.4 GBq (200 mCi) ± 10% at the date and time of administration.

The vial is enclosed within a lead container for protective shielding.

Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with national regulations.

Lutetium-177 may be prepared using two different sources of stable isotopes (either lutetium-176 or ytterbium-176) that require different waste management. Lutetium-177 is prepared using ytterbium-176 ("non-carrier added") unless otherwise communicated on the product batch release certificate.

Manufacturer:
See folding box.

® = registered trademark

Product owner

Advanced Accelerator Applications International SA

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1204 Geneva, Switzerland